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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

19900 MacArthur Blvd., Ste 300
Irvine, California 92715-2445
Telephone (714) 798-7600

January 28, 1998

WL-12-8

WARNING LETTER

Allen Y. Chao, Ph.D.
President
Watson Laboratories, Inc.
311 Bonnie Circle
Corona, California

Dear Dr. Chao:

During an inspection of your pharmaceutical manufacturing facility conducted between November 13 to 21, 1997, our investigators found significant deviations from the Good Manufacturing Practice for Finished Pharmaceuticals regulations (Title 21, Code of Federal Regulations (CFR), Parts 210 and 211). Such deviations cause human drugs manufactured by your company to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (Act).

Our investigation revealed there is no assurance that the methods used in or the facilities and controls used for the manufacture, processing, packing, or holding of your finished pharmaceuticals are in conformance with the GMP requirements as follows:

1. Failure to establish and control written production and process control procedures to ensure proper execution of various production and process control functions [21 CFR 211.100]. For example:

- No particle size or bulk density specifications have been established on granulation or final blends for 19 of 38 products.
- Disintegration specifications were not established before or after process validation.
- No particle size specifications have been established for active ingredients used in 19 of 38 direct compression or wet granulation tablets.
- Process validation studies for products using the fluid bed dryer have no specifications established for Loss on Drying (LOD), particle sizing, and bulk density testing of the granulation.

- The validation studies performed on the Glatt fluid bed drying process did not include the equipment settings used on the validation batches.

2. Failure to establish adequate procedures to assure equipment and utensils are sanitized at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of drugs beyond the official or other established requirements [21 CFR 211.67]. For example:

- Currently, the firm is not performing periodic testing of equipment rinse samples for product residue.

- No environmental or product testing has been performed in Building #1 for detection of hormone contamination from Building #2 which may have been introduced by use of shared equipment, materials, or personnel.

3. Failure to establish sufficient laboratory controls to assure that components, in-process materials and drug products conform to appropriate standards of identity, strength, quality and purity [21 CFR 211.160]. For example:

- The atomic absorption test method has not been validated.

- No determination of cause for the higher than normal dissolution results obtained.

- Discarding and averaging of Out of Specification test results without explanation.

- Failure to investigate Out of Specification test results.

4. Failure to control your established testing program designed to assess the stability characteristics of your drug products [21 CFR 211.166]. For example:

- The inventory records for 2 of 5 studies examined did not accurately reflect the actual number of sample containers in the RT stability chamber.

- The stability study monitoring procedure does not address the length of time that can elapse between final product packaging and placement of the product on stability.

- The stability study monitoring SOP does not define the phrase, "slight change in color which is acceptable", when describing tablet appearance.

- Testing is not always completed in a timely manner.

- The stability indicating HPLC method used for related substances testing of a product has not been fully validated in that the linear range and Limit of Detection/Limit of Quantitation for all known impurities has not been determined.

5. Failure to ensure that batch production and control records include complete information relating to the product and control of each batch of drug products manufactured by your firm [21 CFR 211.188]. For example:

- Master batch and production records are inaccurate and/or incomplete.

  a) No room numbers are documented for rooms used in any manufacturing processes including weighing, blending, drying, tableting or encapsulation, etc.

  b) Recording charts from the Glatt fluid bed dryers are not identified with equipment number.

  c) Documentation of blending shows the timer setting, rather than the actual times when blending was started and completed.

- Master batch records do not include documentation of the amount of active ingredient per dosage unit, in addition to the total amount of active ingredient required for the total batch.

- There is no documentation of corrective actions taken, if any, when the pressure differentials in any manufacturing room fail to meet the limit >0.01". There is no assurance that products manufactured in these rooms were not contaminated with other powders or products during manufacture.

- A batch record is missing documentation of a maintenance repair to the fluid bed dryer during the granulation processing. There is no documentation on the batch record that this process interruption and equipment repair occurred during granulation of this lot.

- No limits have been established for percent rejects allowed after 100% inspection of packaged birth control tablet products.

6. Failure to properly ensure that employees are capable of performing their assigned functions and are familiar with the Good

Manufacturing Practice (GMP) regulation which are commensurate with their intended duties [21 CFR 211.25]. For example, our investigation disclosed that analyst(s) had not received sufficient training in determinative steps in analysis which they have been assigned to perform.

We acknowledge that you have submitted to this office a response concerning our investigator's observations noted on the form FDA 483. This response will be evaluated and communicated to you when our evaluation has been completed.

Our office has significant concerns about the corrective measures undertaken by your company to eliminate the recurrence of the deficiencies disclosed in earlier inspections conducted by our office. Because many of the current deficiencies are similar to earlier deficiencies found at your company, we wish to meet with you and representatives of your company to discuss our concerns.

Please contact Kim Childress, Consumer Safety Officer at 714-798-7732 to arrange a meeting and be prepared to discuss your planned corrective measures at this meeting and the steps to eliminate similar deficiencies in future inspections. Additionally, our office plans to conduct a reinspection of your establish to ensure that the planned corrections have been implemented and we would like to discuss the timeframe that your firm has proposed so our reinspection can be scheduled.

The above listed violations are not intended to be construed as all inclusive of those existing at your firm. It is your responsibility to ensure that all requirements of the Federal Food, Drug, and Cosmetic Act and regulations promulgated thereunder are being met.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Such action includes, but is not limited to, seizure and/or injunction. Federal agencies are advised of the issuance of all warning letters about drugs and devices so that they may take this information into account when considering the award of contracts. Additionally, pending Antibiotic Form 6, NDA, ANDA, or export approval requests may not be approved until the above violations are corrected.

You should notify this office in writing, within 15 working days of receipt of this letter, of the specific steps you plan to take to assure that each of the noted violations will be corrected. Your response should also include an explanation of the specific steps which will be taken to prevent the recurrence of similar violations.

Your reply should be addressed to:

Dannie E. Rowland
Compliance Officer
U.S. Food and Drug Administration
19900 MacArthur Boulevard, Suite 300
Irvine, California 92715-2445

Sincerely,

Elaine C. Messa
District Director

State Department of Public Health
Environmental Health Services
Attn: Chief, Food and Drug Branch
601 North 7th Street
Sacramento, CA 94234